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25 CHARLOTTE SQUARE
EDINBURGH

2nd June, 1919.

THE CO-RELATION OF THE DUCTLESS GLANDS AND THE ONSET OF LABOUR.

by

Colonel F. A.F. Barnardo, C.I.E., I.M.S.

I have read Colonel Barnardo's paper on the above subject, and I am distinctly of opinion that it is an exceptionally good piece of work, and had the writer had sufficient time during the urgency of his service work, it could have been elaborated into a very excellent thesis. Taking into consideration the high quality of the work and the length of time the author has bestowed on experimental studies and research in connection with it, and further considering his excellent record, I am of opinion that this communication should be accepted in lieu of an ordinary thesis.

Embarkation Medical Branch,
No:2, Alexandra Docks,

Bombay (India) Dated 31st Mar.19

From,

Colonel F. A. F. Barnardo,
C.I.E., I.M.S.,

To,

The Dean of the Faculty of Medicine,
University of Edinburgh.

Sir,

I have the honour to lay this applica-
tion before you for your favourable consideration
and recommendation.

I graduated M.B. C.H.B. in the University of Edinburgh in 1899 and proceeded to South Africa on Active Service in the Fife of Forfar Yeomanry as a trooper. On my return in 1902 I appeared for the examination for the Indian Medical Service and passed successfully obtaining the first place. On my first leave Home from India in 1905 I passed the Clinical Examination prescribed for the degree of M.D. Edinburgh University. As winner of the James Scott Scholarship in Midwifery in my graduation year and as Resident Surgeon in the Simpson Memorial Hospital in Edinburgh I took up Midwifery and Diseases of Women as a special subject and now have been working at this branch of Medical Science continuously from that date.

" The onset of Labor" was the special subject in that special branch of Midwifery and Diseases of Women to which I devoted ten years of my experimental studies and research intending to write the Thesis necessary for the degree of M.D.

In May 1914, I had completed the first series of experiments from which I formed the conclusions as detailed in the attached pamphlet which if corroborated will prove to be epoch-making in the Branch of Midwifery.

In August 1914 I was recalled to Military duty and appointed the Medical Railway Transport Officer, Bombay, and subsequently D.A.D.M.S Bombay. In March 1916, I was deputed to proceed to Mesopotamia on special duty. In September 1918, I was selected to accompany Major General T.E.Scott, C.B, D.S.O.,C.I.E., on a special mission to East Africa in connection with Indian Troops. For war services rendered since that time I have been promoted by a Brevet Lieutenant Colonelcy in January 1917 and in June 1918 was awarded a C.I.E. In May 1918 I was granted the rank of Colonel and appointed A.D.M.S.Embarkation Staff, Bombay, which appointment I now hold.

I have been unable during the last five years of War to devote time to writing a Thesis worthy to be submitted for the M.D.degree of the University of Edinburgh (my "Alma Mater") but I venture to submit that the accompanying monograph

may be regarded as evidence of original work of a nature which, had my services not been required for war duty, would have eventuated in the completion of a suitable Thesis.

Under these circumstances I have the honour to request that my inability to submit a Thesis worthy of consideration to qualify for the degree of M.D. has been due to conditions resultant on continuous War service and therefore I have the honour to ask that the accompanying monograph may be held to be equivalent to a Thesis and that the degree of M.D. (in absentia) may be conferred upon me at the next Graduation Ceremony of the University of Edinburgh.

I have the honour to be,

Sir,

Your obedient servant,

J. A. Fleming Barnardo

M.A. M.B.Ch.B. F.R.C.S. M.R.C.P.(Edin.)

Colonel I.M.S.,

h.D-1919.

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By FLEMING BARNARDO, M.R.C.P. (Ed.)

MAJOR, I.M.S

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A FEW notes on some experimental observations, on the co-relation of the ductless glands during pregnancy and factors determining the onset of labour.

I would like to draw attention to a sign denoting the intrauterine death of the fetus, which, as far as I understand, has been, up till now overlooked, *i.e.*, the presence of milk in the mamma, within 3—5 days of the occurrence (according to the period of pregnancy; the earlier the pregnancy is terminated, the later for the milk to appear). This milk is a true milk secretion and not merely a watery colostrum. The advantages of this knowledge concerning the vitality of the fetus in doubtful cases will readily be apparent, when alternatives in operative interference are before the surgeon, in complications during the latter months of

pregnancy. The presence of this true breast secretion, in such cases, is constant and easy to verify. The explanation is more obscure, and it apparently depends entirely on the interaction of the glandular hormones, in the economy of the pregnant mother. This interaction is complex in the non-pregnant state, and has so far been difficult to elucidate, but much light is shed on the correlation of the ductless glands and their hormones by their behaviour during pregnancy, and I might just briefly refer to some known facts regarding this action, with such light as may be thrown upon them, by some experiments of mine continued during the last eight years.

The corpus-luteum of the ovary, as shewn by Blair Bell, Hicks and others, seem to secrete a hormone (lutein) which activates the parathyroids and modifies the excretion of calcium, and causes changes to occur in the mucosa of the uterus, which show themselves clinically as menstruation. The recent researches of Meyer shew that the vascularization, maturation, and retrogression of the corpus-luteum, go hand in hand with the cyclic changes in the uterine mucosa—the maturation occurring with the onset of menstruation. Fellner's experimental work clearly brings out the marked hypertrophy, etc., of the uterine mucosa in non-pregnant uteri, by the injection of extract of ovaries which each contain a corpus-luteum.

As to the uterine mucosa itself, Schröder has recently done much work on the menstrual cycle and changes therein, and he maintains that the secretion of the mucosa reacts in all respects to mucin, and is of opinion that the uterus is not like the ovary, a factory for a special product. This

view of the non-pregnant mucosa is in accordance with all my experiments; but it is very different I find with the pregnant decidual mucosa.

The chorionic tissue of the developing fertilized ovum seem certainly to secrete a specific albumin, (placentin, we may call it) which is activating for the thyroid and the infundibulum; for the thyroid, perhaps, to deal with the anticipated rise in level of endogenous toxins, due to the presence of the developing fetus: for the infundibulum, especially, to call forth the pressor substance to maintain a constant and rich blood supply for the new life, and also undoubtedly to counteract the fall in blood pressure, etc., which would be resultant on the increase in the activated thyroid. This biochemical factor underlying the relation between these two glands, in their simultaneous enlargement, Cushing has called attention to and points out the signs of functional exhaustion of the infundibulum in women who have had repeated pregnancies in the adiposity, loss of hair, and sub-normal temperature, so common in multi-multipara.

This placentin further seems to have an important action on the uterine mucosa itself, by causing an antigen reaction in it, and activating a substance which checks and limits the invasion of the maternal tissues by the fetal villi. This subtance will be absent or deficient in cases of chorio-epithelioma, where the phagocytic power of the fetal epithelium is not checked by the uterine cellular elements, as Haultain long ago pointed out. This uterine hormone (or hysterin) is excited at the outset of the implantation of the ovum by the developing fetal epithelium. Whether it is secreted by the "glande endocrine

myomètriale," described by Anul and Bouin, or not, as yet remains to be verified.

This uterine albumin (or hysterin) is inhibitory to ovarian activity, and prevents its influence on the rest of the uterine mucosa, causing clinically the characteristic amenorrhœa of pregnancy. It is this uterine secretion that the lutein in the corpus-luteum during pregnancy and the lutein cell border formation of Meyer, actively functionates during pregnancy. Fichera, however, maintains that the hyperplasia of the infundibulum following oophorectomy, is analogous to that following pregnancy, and believes that the changes in its anterior lobe are due to ovarian insufficiency. The ovarian insufficiency here may be caused by the inhibitory action of the uterine hormone.

It is this uterine albumin, or hysterin, that plays an important part in mammary activity. Though most of the products seem to be activated and held in neutralization by the placental albumin, some escapes into the general circulation and is then available for the activation of the breast tissue, giving rise to the well-known breast enlargement in pregnancy.

On expulsion of the placenta in the third stage of labour the placental albumin is then extra-corporeal, and is not neutralizable; the uterine albumin floods the circulation and activates the breast, which increases rapidly in size and function, giving clinically the well-known rush of milk to the breast on the 2nd or 3rd day.

On the intrauterine death of the fetus a similar occurrence probably takes place. The secretion of placental albumin has ceased, the uterine hormone is not neutralized; it escapes

into the circulation and activates the breast follicles to rapid growth and maturation, and milk flow is the result.

The association of mammary activity with pregnancy and parturition has been the theme of many explanatory papers indeed, but, so far in the existing theories, there is little of continuity. I may just draw attention to a few points which my experimental work has brought out.

The hyperplasia of the lobular acini of the breast in pregnancy cannot be in response to a nervous stimulus, as neither pilocarpine nor atropin have any effect whatever on it, as judged by the milk secretion. Mechanical stimuli are important, but the response of the breast to these, as massage, suckling, etc., brings not a true secretion, but only an increased flow, consequent on the reflex contraction of muscular fibres round the lacteal ducts. In this connection, the habits of young animals are interesting in their endeavour to stimulate maternal secretion mechanically; as the pawing and kneading of the breasts, by puppies and kittens and humans, and the punching of the udder by calves, etc., etc.

Niklas has recently suggested the view that the stimulus is probably a hormone. He is uncertain as to its factory of origin. It may be, he says, in the ovary thyroid, thymus, hypophysis, placenta (Fetal) or the breast tissue itself. He inclines to the view that the placental tissue is the seat of the galactagogue hormone. I cannot experimentally corroborate this. But I find there is the most marked distinction, between the action of glandular extracts, on the resting breast and the lactating one.

As regards the resting and non-lactating breast, I have found no response whatever, either measured by volume or secretion, by the use intravenously of pituitary, thyroid, ovarian or thymus extracts (of the same species). The same exactly resulted by use of mammary extract (of either resting or lactating glands). Pregnant uterine extract caused some activity, within 24 hours, in the breast, *i.e.* an increase of volume, and some slight flow of milk on the 2nd day. Non-pregnant uterine extract caused no activity whatever. Placental extract sometimes caused activity and sometimes did not, probably, as we shall see, due to its chance content of any uterine extracts.

But as to the lactating gland itself, results were somewhat varied, but the summary may be briefly stated. Extracts of thyroid, thymus, mamma (lactating or resting) had no activating influence whatever. Pituitary extracts gave a fairly constant degree of increase, but the breast decreased in volume, while the specific gravity of the contents was lowered. In no case did pituitary extract increase the milk flow in cases where lactation had failed (in cases of sepsis, shock, etc.) or was failing. Placental extract, unwashed, gave a greater activating extract than placental extract washed, but nothing like so much as pituitrin. This seemed to indicate, as in the Abderhalden pregnancy reaction, the presence in unwashed placental tissue, of some substance which was not in the tissue when washed. For by that reaction, one can clearly show the existence of a specific albumin in the maternal blood, which will react to placental albumin. Abderhalden's technique is extremely

exact and he lays great stress on the washing of the placental tissue before making the extract. This is virtually removing most of the maternal cellular elements and their products. Most of the variations, it would thus appear in the verification reports of observers, would appear to have resulted from the non-adherence to the careful technique prescribed, and in especially the careful washing of the placental tissue. For the more maternal albumin there is present in the placental extract, the less will the reaction of the maternal blood to it, hence the necessity of its removal to get accurate and consistent results.

This would appear to suggest the uterine cellular elements as being the factory of the galactagogue hormone. And I found in lactating bitches, the greatest activator of mammary activity, to be the extract of pregnant or puerperal uterus of the same species (a resting uterus gave no response). If intravenously injected into a lactating bitch, the appearance of an increase in flow of milk could be noted in 8—10 minutes, and the measure of the increase was 15—20 fold. If the puerperal uterine extract be intravenously injected into a pregnant bitch, the milk secretion would be apparent in 30—32 hours, gradually decreasing after 72 hours if the injection be not repeated.

But has the activated breast itself then no specific secretion of its own? Seitz would have it that there is no internal secretion proved for the mammary gland. Others, such as Walcher, maintain that the factory for the toxins causing eclampsia is found in the mammary gland, and he advises emptying the breasts or amputation as a means of treatment. This position is denied

by Wilson, who classifies the mammary theory of eclampsia as a specious one.

Whatever be the action of the mammary secretion on metabolism generally, when excessive or perverted in the direction of eclampsia, it can be easily demonstrated to have a very definite action on the pregnant uterus itself.

It would seem that the uterine contractions and retractions, which are continuous throughout pregnancy (clinically known as Braxton Hicks' sign) are the result of the mammary hormone being accumulated, under activation from the uterus, and being at intervals discharged into the circulation, each discharge is followed by a uterine contraction and as labour is only the end result of the gradual lengthening and strengthening of these contractions and retractions, this mammary hormone, by ever-increasing discharges into the blood, would seem to be the primary factor in the onset of labour. Further, when the uterine contractions are so great as to cause oozing of greater and greater quantities of uterine mamma-activating substance into the circulation, the hypophysis is greatly stimulated and uterine contraction is much auxiliated by its pressor action. The hypophyseal extract causes the contraction of the muscular fibres in the mamma and in the absence of milk secretion, forces an ever increasing amount of mammary hormone into the circulation. This, again, reacts on the uterus to a further increase of contractions, and thus we have the uterus and mamma commencing the process of labour, and when this uterine contraction becomes strong enough to force a sufficient percentage of uterine hormone into the circulation to activate the hypophysis, the

latter, too, helps in the process, and the action of the hypophysis thus is seen to be at its greatest, when the reciprocal activation of uterus and mamma is at its highest point, *i.e.*, towards the end of labour.

Thus, Löfqvist has shewn that pituitrin will not stimulate contractions in a uterus, which is not in labour already; at first its action is only weak and becomes maximal only at the end of labour. No amount of medicinal substance as berberine, ergot, causing simple uterine muscular contraction, can ever cause the onset of labour. The emptying of the uterine cavity and the lengthening of the periods of contraction depends on the periods of relaxation, *i.e.*, on the alternation of contraction and retraction. If this were the result of hypophyseal extract alone, continued uterine contraction would be the result, owing to its pressor action on muscular tissue and death of the fetus would naturally result. The difference between the action of ergot and the mammary hormone is, that ergot causes a tetanic or continuous contraction of the muscular fibres with no relaxation, and hence is useful in post-partum hæmorrhage, as such hæmorrhage occurs chiefly in the periods of relaxation. But the mammary hormone at first alone, and later the mammary, aided by the pituitary hormone in labour, causes the lengthening of the contractions and the shortening of the periods of relaxation; and hence pituitrin is more useful in inertia uteri, rather than in post-partum hæmorrhage, as, owing to the existence of periods of relaxation (short as they may be), its use is not so effective, as a hæmostatic, as ergot. But as Ballantyne has recently pointed out, the use of

pituitrin at present is mainly empirical, and its therapeutics have outrun our knowledge of its pharmacological action.

Schäfer has, however, in his recent exposition of the function of the pituitary body, found a hormone in the posterior lobe, activating secretion (apart from mere muscular stimulation) in the lactating mammary gland, and Herring, too, has obtained a pituitary hormone from the skate, stimulating the mamma, without either influencing the circulation on the kidney.

Heaney, however, does not acquiesce in these views, and has shewn that no amount of pituitrin will increase the manufacture of actual milk secretion, and he still maintains that the galactogogue action is entirely a muscular one.

With this view of Heaney's my experiments are inclined to agree. I can find no actual increase of milk secretion, only an increase of milk flow; and, judging from the failure of pituitrin to stimulate the rapidly failing lactation in cases of shock, sepsis, etc., I believe that its galactogogue action depends on (1) its stimulation of the uterus to contraction, thus forcing out an increased amount of uterine hormone into the circulation of which hormone is the activating agent for the mamma, (2) its stimulation of non-striped muscle fibres in the mamma itself. The pituitary extract is thus a secondary and not a primary galactogogue, and while the enlargement of the pituitary body and mamma is due primarily to the uterus, still the former, by causing the contraction of the non-striped muscle fibre of both the latter, controls the biochemical relation between the two. Moreover, this galactogogue hormone too, by the researches of Ott, Schott and Mackenzie is corroborated as

being found in the posterior lobe of the hypophysis, in common with the pressor substance, and not in the anterior lobe, where one would expect it, if it were a primary secretion (or another specific property of the hypophysis itself).

In the puerperium, the continuance of the activity of the breasts, leads to continuance of uterine contraction and retraction and hence more rapid involution; and so two popular ideas seem actually to have a physiological basis, *i.e.*, (1) the possibility of checking post-partum hæmorrhage by massage of the breasts, (2) the more rapid involution of the uterus, if the child is suckled.

Further, as long as lactation is going on, it is rare for ovulation and menstruation to commence, probably, for, as long as the uterine hormone is present in the puerperal uterus, it is not only activating the breasts, but also inhibiting the ovaries.

The metabolism of the body under the direction of the ductless glandular system is thus made more obvious by the many suggestions afforded by its behaviour in pregnancy, and as Blair Bell has pointed out, most of the confusion and contradiction in the work, so far done, has been due to the neglect of the principle, that the essential processes of life, *i.e.*, the individual metabolism and the reproductive metabolism, are not only interdependent, but are actually one and the same, and we can thus thoroughly agree with his aphorism :—"*Propter secretiones internas totas, mulier est quod est.*"